REMARKS

Claims 34-38 and 40-45 are pending in the application and claims 1-33 and 39 have been canceled. Claims 44-45 have been added. Support for added claims 44-45 can be found in the specification as filed on page 4, second to last paragraph.

In the February 15, 2007 Office Action, claims 34-38 and 40-43 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Krebber et al. (1997) *J. Mol. Biol.* 268:607-618 (cited in the IDS) as evidenced by Weiner and Chun (1997) *J. of Comparative Neurology* 381(2):130-142 in view of Mersmann et al. (1998) *J. of Immunological Methods* 220:51-58. The specific grounds for rejection, and applicants' response thereto, are set forth in detail below.

Rejections Under 35 U.S.C. §103(a)

Claims 34-38 and 40-43 are rejected under 35 U.S.C. §103 as obvious over Krebber, as evidenced by Weiner and Chun, in view of Mersmann. Specifically, the Examiner asserts that Krebber teaches nucleic acids encoding a gene III N-terminal protein linked to a 10 amino acid purification tag, but admits that Krebber fails to disclose nucleic acids encoding the gene III fragment linked to a sequence that is 100 to 2000 base pairs long. This deficiency allegedly is remedied by Mersmann, which purportedly discloses nucleic acids encoding gene III linked to antibody chains where the nucleic acid encoding the antibody chain is 100-2000 base pairs long.

Applicants August 15, 2007, response explained why the Examiner's obviousness analysis was flawed. In reply, the Examiner stated in the August 20, 2007, Advisory Action that:

> [O]ne of ordinary skill in the art is taught by prior art that eukaryotic genomic fragments fused to gene III protein are expressed in the bacterial expression system. If one of ordinary skill in the art desired to have their fusion protein collect in inclusion bodies then they would choose to fuse their gene of interest to a construct taught by Krebber et al. which lacks the signal sequence thus ensuring that the expressed protein would collect in inclusion bodies. As courts have reiterated several times in KSR decision it would be common sense for one of ordinary skill to combine teachings of Mersmann et al. with the teachings of Krebber et al. if they wanted to.

Advisory Action at page 2. Applicants respectfully submit that these assertions apply an incorrect legal standard to the analysis here and fail to rectify the flaws of the prior office action. Accordingly, applicants respectfully traverse.

The USPTO recently set forth guidelines for examining applications in light of the recent Supreme Court decision in KSR v. Teleflex. "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*" 72 FR 57526 (2007)("The PTO Guidelines"). The PTO Guidelines state that

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn* "stated that " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

Id. at 57528-9. Here the Examiner's statements that it would have been "common sense" to combine the teachings of Mersmann and Krebber fail to meet the standard set forth in *KSR* and the PTO Guidelines. Accordingly, applicants respectfully traverse the rejection.

The instant claims recite a nucleic acid molecule encoding a fusion protein comprising the first N-terminal domain of the gene III protein of filamentous phage and a (poly)peptide which is encoded by a nucleic acid sequence comprised in a genomic DNA fragment or an expressed sequence tag (EST). The gene III fusion partner is derived from a eukaryotic cell and is 100-2000 base pairs in length. The fusion protein lacks a signal sequence for transport of the fusion protein to the bacterial periplasm. The fusion proteins are useful, for example, for generating antibodies that bind to the intact protein in a cell.

By stark contrast, Krebber deals almost exclusively with gene III fusions that contain a signal sequence, where the fusion protein is exported to the bacterial periplasm once produced. Krebber also describes a nucleic acid encoding an N-terminal domain of gene III attached to a short 10-amino acid histidine tag ("His-tag") having the sequence SGCPHHHHH (see, Figure 3d), for purifying the gene III protein.[1] This construct lacks a signal sequence and is relied upon by the Examiner for a suggestion to make gene III fusions that lack a signal sequence.

[1] Indeed, the Examiner acknowledges that histidine tags are used simply for purification purposes, stating that "[t]he poly (HHHHH) histidine tails are well known tags used in the art. These histidine tags are fused to the protein to facilitate the subsequent purification of the fusion protein in combination with immobilized metal ion affinity chromatography." Office action at page 4.

However, the His-tag is not encoded by either a genomic DNA fragment or an expressed sequence tag (EST), nor is it 100-2000 base pairs in length – rather, it is encoded by 30 base pairs of DNA. The Examiner has selected a portion of this sequence – SGCPH – without explanation as to why such a fragment was selected, and asserts that it meets the criteria for a sequence encoded by a genomic fragment or an EST because the sequence SGCPH can be found in databases of the genome. Tellingly, the Examiner is silent with regard to whether the entire sequence of SGCPHHHHHH is found in any genomic fragment or EST. It is improper for the Examiner to ignore the entire sequence used by Krebber in trying to construct an argument that one skilled in the art would recognize *part* of Krebber's peptide as being encoded by a genomic DNA or an EST. There is no evidence that one skilled in the art would ever recognize the SGCPHHHHHH sequence as being encoded by either a genomic DNA sequence or an EST.

Moreover, it is clear from Krebber that, with respect to the His-tag-gene III construct, it is *the gene III domain* that is of interest, and not the His-tag, which is merely a purification tool. Indeed, the legend to Figure 3d states that the "gIIIp domains N1, N2, and N1-N2 were independently expressed without signal sequence and purified. * * A hexahistidine purification tail is engineered to the C terminus as indicated, which also contains a single cysteine, to which ligands can be chemically attached." One of ordinary skill in the art reading Krebber would not have had any motivation to modify Krebber to replace the His-tag with a much longer peptide encoded by a genomic DNA fragment or an EST, since this would have been of no value in purifying the gene III fragment. Nothing in Krebber teaches or suggests using a fusion partner for the gene III protein that is longer than the short purification tag while simultaneously lacking a signal sequence. In sum, Krebber provides no motivation whatsoever to one skilled in the art to prepare *any* construct encoding a gene III fragment and a genomic DNA fragment or EST, regardless of the length of the genomic fragment or EST

While acknowledging that Krebber fails to teach gene III fusions where the fusion partner has the length recited in the instant claims, the Examiner asserts that Mersmann remedies this deficiency by teaching fusions with antibody fragments having the length recited in the instant claims. However, the Examiner is combining apples and oranges: one of ordinary skill in the art would not have been motivated to combine the nucleic acid disclosed by Krebber, where the construct lacks a signal sequence, with the nucleic acid disclosed by Mersmann, where all the constructs contain a signal sequence. The instant claims explicitly recite that the claimed nucleic

acid molecule lacks a signal sequence for transport of the fusion protein to the bacterial periplasm. Mersmann provides no suggestion whatsoever to prepare a construct lacking a signal sequence – indeed, the opposite is true since Mersmann deals with classic display methodology where gene III fusion proteins are transported to the bacterial periplasm to combine with other phage proteins to make phage particles. In this sense, Mersmann can be seen as teaching away from the instantly claimed invention by suggesting that gene III fusion proteins should contain a signal sequence.

In addressing these arguments, the Examiner in the Advisory Action states that "it would be common sense for one of ordinary skill to combine teachings of Mersmann et al., with the teachings of Krebber et al. *if they wanted to*." (Emphasis supplied). The Examiner also states that "*[i]f* one of ordinary skill in the art *desired* to have their fusion protein collect in inclusion bodies then they would choose to fuse their gene of interest to a construct taught by Krebber et al. which lacks the signal sequence thus ensuring that the expressed protein would collect in inclusion bodies." (Emphasis supplied). However, the Examiner's appeal to "common sense" here fails to rise the level of "the clear articulation of the reason(s) why the claimed invention would have been obvious" required by *KSR* and the PTO Guidelines. Indeed, the Examiner's assertions are precisely the kind of conclusory assertions that are barred by *KSR* and the Guidelines.

Moreover, the portions of the text from the Advisory Action italicized above demonstrate that the Examiner is applying improper hindsight reasoning in arriving at the instant rejection. The Examiner states that "if" one of ordinary skill in the art sought to make fusion proteins in inclusion bodies it would be "common sense" to combine Mersmann and Krebber "if they wanted to." But why would they want to? The Examiner does not say, and neither do the cited references. The only suggestion to fuse genomic DNA fragments or ESTs to nucleic acid encoding the first N-terminal domain of the gene III protein of filamentous phage is found in the specification of the instant application. Even if the Examiner were correct that Mersmann and Krebber somehow can be combined, the absence of any rationale for making the combination makes the instant rejection fatally flawed. Accordingly, withdrawal of the rejection respectfully is requested.

Finally, it is axiomatic that it is improper to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full

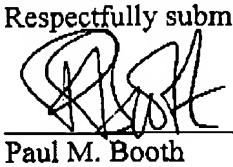
appreciation of what such reference fairly suggests to one skilled in the art. In the instant case, the combination of Krebber and Mersmann is improper because it ignores the key distinction that the fusion proteins described by Mersmann all contain a signal sequence. For at least these reasons, there would have been no motivation for one of ordinary skill in the art to combine Mersmann with Krebber and the rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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